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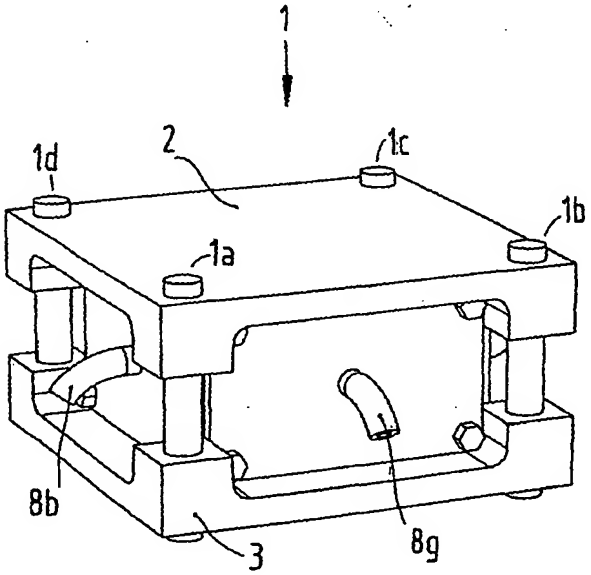
(54) Title: BLOOD PROCESSING DEVICE



(57) Abstract: The present invention relates to a device, comprising: - a first plate provided with a number of first channels in a first direction for transporting a fluid such as blood therein; - a second plate close to the first plate provided with a number of second channels in a second direction for transporting one or more gases or a mixture of gaseous medium therein; and -a gas-permeable membrane arranged between the first and second channels.

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BLOOD PROCESSING DEVICE

In the performing of some medical operations, such as open heart operations, it is necessary to take over the lung function temporarily by means of equipment. Oxygenators have been developed for this purpose. These devices are able to absorb carbon dioxide from the blood and to add oxygen to the blood.

The already existing oxygenators have a number of drawbacks, however. The priming volume of the blood required to work with an oxygenator is very large in the existing devices. In the case of humans 10% of the blood volume of an adult is required for the priming volume. Another drawback is that the ratio of the priming volume and the effective contact surface that can be used for the transfer of oxygen and carbon dioxide is small.

In order to obviate the stated drawbacks the present invention provides a blood processing device, comprising:

- a first plate provided with a number of first channels in a first direction for transporting blood therein;
- a second plate close to the first plate provided with a number of second channels in a second direction for transporting gases therein;
- a gas-permeable membrane arranged between the first and second channels.

An advantage of the present invention is a relatively large ratio of the priming volume and the contact surface. It is further possible to achieve a very low priming volume by keeping the dimensioning of the plates and the channels very small. It hereby even becomes possible to connect small mammals, such as rats

or children, to the blood processing device without external blood having to be added for this purpose.

Such a device can be applied with the same advantages for performing for instance blood dialysis. Instead of gases a flushing liquid is herein passed through the channels whereby substances are exchanged with the blood in the other channels. This application can also be used in further embodiments which are described hereinbelow, wherein for 'gases' can be read 'liquids'. In this application the membranes are suitable for exchanging contaminating substances occurring in blood.

A preferred embodiment further provides a device as specified above wherein channels in one direction debouch at the ends thereof in a supply or discharge chamber which is bounded on one side by the ends of the plates with the channel ends, and to which is connected a supply or discharge of respectively the fluid and the gases, wherein each channel is directly connected to the supply or discharge chambers. An advantage hereof is that in very simple manner a uniform blood flow is obtained through all channels wherein the blood is distributed uniformly over all the channels. In a further embodiment described hereinbelow, a plurality of pairs of plates is used and this embodiment with chambers has the advantage that all channels of all plates are provided according to this embodiment with a uniform quantity of blood in very simple manner.

The channels are preferably arranged such that the angle between the channels is situated at an angle between 0 and 180°. An embodiment with an angle of 180°, i.e. the channels are parallel and the streams of the fluids flowing through the channels flow in opposing directions, has the advantage that the differences in concentration of the substances to be exchanged between

the two fluids via the membrane are maximal during the whole progress through the channels. An embodiment with an angle of 90° has the advantage that it is relatively simple to manufacture, since only one chamber need be arranged per side.

A further preferred embodiment of the present invention has the feature that the angle between the first and the second direction is an angle in an interval of 30-90°. An embodiment with an angle of for instance 30° can be applied for a plurality of flow directions, as in the following embodiment.

A further embodiment provides third plates with third channels in a third direction for transporting cooling agents or heating means therein. By transporting cooling agents it is possible to cool the blood during the treatment. By making use of a third direction the blood and the air do not come into contact with the cooling agents. Heating means are applied in similar manner to heat the blood.

A further preferred embodiment of the present invention includes the feature that the plates and the membranes are manufactured from a biocompatible material. It is further recommended that the membranes are made of a microporous material to allow passage of the gases, such as oxygen and carbon dioxide. An example of such a microporous material is polypropylene. Examples of biocompatible materials are RVS 316 (DIN 1.4401), RVS 316L (DIN 1.4404), ASTM F6795 or ASTM F1314-95, wherein the RVS codes are AISI codes. The plates can be manufactured from these alloys. Plastics have properties which are very advantageous in the manufacture of the plates. Manufacturing techniques which can be used to manufacture small channels such as are suitable for application in a device according to the present invention are roller embossing, UV embossing

and injection moulding. By applying such techniques in the manufacture of channel structures according to the present invention it becomes possible to apply such structures economically in a device according to the present invention. Such devices with channel structures are usually suitable for once-only use. Now that these technologies can be applied advantageously to the manufacture of channel structures according to the invention, it is possible to apply such channel structures in economic manner in devices for one-only use.

A further embodiment of the present invention comprises one or more third plates comprising third channels in a third direction for cooling or heating the device. A significant advantage hereof is that the temperature of the blood can be varied during the treatment. This cooling or heating can take place by supplying a cooling or heating medium through the third channels. It is possible to add the third plates in the same ratio as first and second plates of the device, or in a higher or lower ratio. It may suffice for instance to add a third plate alternately via ten first and second plates for the purpose of cooling or heating.

A further preferred embodiment of the present invention comprises a blood processing device wherein the first plate comprises a first channel on one side and comprises a second channel on the other side. This embodiment has the advantage that, among other things, material and space can be saved by applying in one plate the functions of two separate plates.

A further preferred embodiment of the present invention comprises a stacking of the first plates, second plates and membranes for increasing the treatment capacity of the device. This treatment capacity is related inter alia to the size of the contact surface

between the blood for treating and the gas for treating. On this contact surface the blood is separated from the gas by the membrane. The contact surface is situated at the intersections of the first channels and the second channels. The larger the contact surface available for passage of the gases, such as oxygen and carbon dioxide, the more gas can be exchanged. This contact surface can be enlarged by using or adding to the device more stacks of first and second plates with membranes therebetween. Another option for enlarging the contact surface is to increase the width of the plates, whereby more channels become possible per plate. In other words, the treatment capacity of the device can be varied by varying the number of plates and the size of the plates.

There is further provided the possibility of the plates and membranes being contained in a housing. A further preferred embodiment hereof is that the housing holds the membranes and the plates pressed against each other. For this purpose the upper side and the underside of the housing can hold a stack of plates and membranes clamped and the side walls of the housing can be clamped against the stack of plates and membranes. Such a method of constructing the device is one possibility of keeping the flows of gas, blood and cooling agents separated other than via the membranes.

In a further preferred embodiment of the present invention the membranes are at least permeable to oxygen and carbon dioxide. The advantage hereof is that the treatment can at least have an oxygen- and carbon dioxide-exchanging effect.

There is further provided a thickness of the plates of for instance 100 to 200 µm and a depth of the channels of 20 to 70 µm and a width of the channels of 50 to 250 µm. These dimensions have the advantage that the Reynolds number, the pressure drop and the shear

stress, which influence the blood for treating, come to lie within acceptable limits. Typical values for the Reynolds number are 0.21 to 0.37. For the pressure drop 4700 to 8200 Pa and for the shear stress 3.6 to 6.4 N/m^2, which is acceptable since blood is only damaged at a shear stress above 15 N/m^2 according to "red all Rheology", M Bessis et al, NY.

A further preferred embodiment of the present invention has the feature that the first direction and the second direction or the third direction and the second direction lie in the interval between 10° and 45°. This embodiment can further have the feature that the largest angle between the first direction and the second direction or the third direction and the second direction lies in the interval between 45° and 90°. These features have the particular advantage that cooling can take place and use can be made of a minimal quantity of blood volume. Another preferred embodiment of the present invention comprises a method for treating blood using a blood processing device according to one or more of the above described embodiments. A further embodiment provides for the assembly of a blood processing device according to one or more of claims 1 to 15, comprising steps for stacking plates and membranes.

According to a further aspect, the present invention provides a method for manufacturing an above described plate for use in the above described device comprising steps for arranging micro-ridges in a plate material.

Arranging of the ridges is preferably carried out by means of hot embossing or roller embossing. Roller embossing is a variant of hot embossing wherein a drum with the profile of the ridges presses the ridges into the appropriate plate material at a predetermined

temperature by means of the profile. The use of a drum has the advantage that it is possible to work in a continuous process. Under some conditions hot embossing can however likewise have advantages, such as utilizing machine capacity. Tests have shown that very suitable plates could be manufactured using hot embossing.

In a further embodiment plates are provided with ridges for use in a device according to the invention by means of UV embossing. This technique, per se known from optical applications, is suitable for arranging ridges in plate material. Use is herein made of plastics which cure under the influence of UV light.

In another embodiment use is made of injection moulding for arranging the ridges, which is also a suitable mass production method for manufacturing plates according to the present invention in advantageous manner. A form of micro-extrusion produces the appropriate ridges in such a method.

Further advantages, features and details of the present invention will become apparent upon reading of the following description of a preferred embodiment with reference to the associated figures, in which:

- figure 1 is a perspective view of an assembled embodiment of the present invention;
- figure 2 is an exploded view in perspective of the embodiment of figure 1;
- figure 3 is a perspective view of an embodiment of the plates according to the present invention;
- figure 4 is a perspective view of another embodiment of the plates according to the present invention;
- figure 5 is a perspective view of a third embodiment of the plates according to the present invention;

- figure 6 is a perspective view of a fourth embodiment of plates according to the present invention;
- figure 7 is a perspective view of a fifth embodiment of plates according to the present invention;
- figure 8 is an exploded schematic representation in perspective of a further embodiment according to the present invention;
- figure 9 is a view in perspective of the embodiment of figure 8;
- figure 10 is an exploded schematic representation in perspective of a further embodiment according to the present invention;
- figure 11 is a perspective view of the embodiment of figure 10.

An embodiment of the present invention (figure 1, 2) is a blood oxygenator with a very small so-called priming volume or operating volume, wherein the quantity lies in the order of magnitude of several millilitres, around 3 ml for the embodiment described here. Using the present invention this volume can be readily increased by using a plurality of modules according to the embodiment described here or by using larger modules.

A housing of oxygenator 1 comprises an upper plate 2 and a lower plate 3 fastened thereto with screw bolts 1a - 1d. The housing furthermore comprises four side walls 4, 5, 6, 7, which are thicker on the inside along the edges than in a middle part for the purpose of allowing passage of blood and gas. Side walls 4 and 6 respectively 5 and 7 are pressed toward each other by means of screw bolts 5a - 5d respectively 6a - 6d. Although the above described construction is very suitable and is applied in a prototype, other designs of the housing will be preferable for mass production, such as for instance glueing, snap connections and the like.

Plates 4 and 6 are further provided with an opening for blood tubes 8b and plates 5 and 7 are provided with an opening for gas tubes 8g. These tubes are intended for feed and discharge of blood respectively gas. Situated inside the housing are stacks of plates 11 and 12 with membranes 13 therebetween. In plates 11 are arranged channels for transporting oxygen gases and in plates 12 are arranged channels for transporting blood. The membrane 13 separating the channels is gas-permeable.

In this embodiment the upper and lower plate are manufactured from polypropylene which is inexpensive and simple to process. Both plates are preferably as mutually symmetrical as possible. Using the screw bolts the stack of membranes and plates is fixed and clamped between the plates of the housing so as to enable the realization of a good sealing.

In this embodiment the side walls are manufactured from polycarbonate. Polycarbonate is transparent, whereby possible leakages can be easily located visually. Slotted holes (not shown) are arranged in the side walls to make the housing suitable for various stacking heights of the membranes and plates.

A seal (not shown) is further provided between the side walls and the edges of the plates. It is important that this sealing material is not too hard, since a hard sealing material requires a greater biasing force for a good sealing. The biasing force should however be minimal in order to limit or prevent deformation of stacks. Used as seal in this embodiment (in a first prototype) is intertwined teflon tape combined with vaseline. However, many types of seal could be used here, such as for instance sealing rings, gaskets or glueing.

As can be seen in figure 3, channels 14a are formed by plate 11 and channel partitions 14. Channels 15a are formed by plates 12 and elevations 15 thereof. Blood flow B flows through channels 14a and gas flow G flows through channels 15a. Gas is then exchanged between the gas flow and the blood flow through membrane 13. This is an exchange of oxygen from the gas flow to the blood flow and an exchange of carbon dioxide from the blood flow to the gas flow. It is self-evident here that the gas flow comprises at least oxygen and that the blood flow comprises at least carbon dioxide.

Since the channels have very small dimensions and the membranes and the plates are very thin, it is possible to arrange a stack of many plates and membranes in the oxygenator. In the present embodiment plates of 0.12 mm and membranes of 0.035 mm are used, wherein the membranes consist of microporous polypropylene. In the present embodiment the channels have a width of 100 µm and a depth of 50 µm, wherein the ridges have a width of 50 µm and a height of 50 µm. This assumes the plates as shown in figure 2a. There are therefore always two plates and one membrane required for a proper operation of a combination hereof. Further prototypes were provided for test purposes with channels having a width of 200 µm.

Another embodiment, that of figure 4, provides channels on both sides of the plates which lie crosswise of each other. In this embodiment the membranes and the plates can be stacked alternately for the exchange of oxygen and carbon dioxide in the blood. An advantage of this embodiment is that the stacking becomes easier and that space can be saved. A third embodiment (figure 5) provides that the membrane forms part of the plates or that the plates are manufactured from the membrane material. In the first case the rear wall 13d of plates

11b consists of the gas-permeable material. In the second case the whole plate consists of the membrane material. The advantages of this embodiment are that gases can be exchanged along two sides of the channels, which on the one hand makes it possible to reduce the number of channels and on the other makes it possible to exchange more gases with the same quantity of blood.

This embodiment is advantageous from the viewpoint of production technique and cost, since the plates can be manufactured from for instance polypropylene. In this embodiment the plates have a channel/throughflow function as well as a membrane function. By means of a process such as for instance hot embossing these plates 11 and 12 can be produced inexpensively and accurately. Further manufacturing methods which can be made specifically suitable for mass production of plates are described below.

Instead of having rectangular plates with two flow directions, a particular embodiment (figure 6) consists of hexagonal plates 31, 32 and 34 with a hexagonal membrane 33. In this embodiment the channels 35a of plate 32 and 36a of plate 31 serve for passage of blood respectively gases in similar manner as in previous embodiments, wherein membrane 33 provides the exchange. A plate 34 is also provided with channels 37a for admitting an additional flow L which can be used for cooling and/or heating. Also provided in this embodiment are partitions 35, 36 and 37 which, together with the respective plates, form the channels.

Because in the case of a rectangular embodiment of figure 6 a higher blood volume is required per contact surface between channels 36a and 34a, another rectangular embodiment (figure 7) is provided having short blood channels 35a and longer gas channels 36a and cooling liquid channels 37a. An advantage hereof is that

there is an equally large contact surface between the blood and gas channels as in the embodiments of figure 2. Although more gas and cooling liquid volume is required, this can be supplied in large quantities, while the quantity of blood available in a body of a human or animal is limited. Certainly in the case of small animals or children the quantity of blood available is small.

In a further embodiment (fig. 8,9) the flow channels or ridges in the plates are embodied in a different manner. Two plates for the purpose of transporting air and blood are herein provided in channels on the sides facing each other. The view of figure 9 shows the inlet for blood 43 and the inlet for gas 41. Figure 8 shows how these channels are designed by means of bends or angles so as to create a large contact surface between the blood and gas channels. This contact surface is separated by membrane 47.

In this embodiment the gas channels run from inlet 41 to gas outlet 42. The blood channels run from blood inlet 43, which is situated substantially at top left in figure 8, to blood outlet 44 at bottom right. Because in this embodiment the ends of the blood and air channels are situated on one side of the plates it becomes possible to also equip a square embodiment with channels with a cooling system. For this purpose plate 53 is provided with water channels, as can be seen in figure 8, with inlet openings 45 on the left-hand side and outlet openings 46 on the right-hand side. If stacks of plates are applied in similar manner as in the embodiments according to for instance figure 3, it also becomes possible in the embodiments of for instance figure 1 to provide all channels with blood, oxygen or water by means of one supply chamber which is formed on the one hand by the stack of plates with the openings of

the channels and on the other by side walls 4,5,6,7 of the housing. For such an embodiment sealing means are of course also necessary to mutually separate or seal the chambers.

In similar manner a channel geometry is shown in the embodiment of figures 10 and 11. The blood channels in plate 10 herein run from the left-hand side of plate stack 50 from blood inlet 61 to blood outlets 62 at the top right-hand and bottom right-hand side of plate stack 50. In similar manner the air channels run from the right-hand side of the plate stack, from air inlet 63 to the bottom left-hand and top left-hand side of the plate stack to air outlet 64. These air channels are arranged in plate 54. A membrane 57 is arranged between plate 54 and 55 for the purpose of the oxygen and carbon dioxide exchange. This embodiment is also provided with cooling plates 56 through which run water channels 66. These water channels run from water inlet 65 on the upper side to water outlet 66 on the underside.

Owing to this arrangement of water, blood and gas inlet and outlet, it is likewise possible to embody the channel inlet and channel outlet by means of a chamber which in very simple manner provides all channels of one type with sufficient supply and discharge. A chamber is arranged for this purpose round blood inlet 61 and gas inlet 63 of all channels. On the upper side and underside of plate stack 50 there are arranged in each case three chambers, respectively for air outlet 64, water inlet 65 and water outlet 66 and blood outlet 62. By making use of such inlet and outlet chambers, all chambers can also be provided in this embodiment with a sufficient supply and discharge in very simple manner. An advantage of this embodiment is that all feeds and discharges are arranged on either side of the device,

whereby in simple manner the device can for instance be dimensioned in many formats and capacities.

The present invention is not limited to the described embodiments; the rights sought are defined by the following claims.

CLAIMS

1. Device, comprising:

- a housing;

- a first plate provided with a number of first channels in a first direction for transporting a fluid such as blood therein;

- a second plate close to the first plate provided with a number of second channels in a second direction for transporting one or more gases or a mixture of gaseous medium therein;

- a gas-permeable membrane arranged between the first and second channels.

2. Device as claimed in claim 1, wherein channels in one direction debouch at the ends thereof in a supply or discharge chamber which is bounded on one side by the ends of the plates with the channel ends, and which is further bounded by at least one wall to which is connected a supply or discharge of respectively the fluid and the gases, wherein each channel is directly connected to the supply or discharge chambers.

3. Device as claimed in claim 1 or 2, wherein the first and second direction are situated in an interval between 0° and 180°.

4. Device as claimed in claim 1, 2 or 3, wherein the angle between the first and the second direction is an angle in the interval of 30-90°.

5. Device as claimed in one or more of the foregoing claims, wherein there are provided third plates with third channels in a third direction for transporting cooling agents therein.

6. Device as claimed in one or more of the foregoing claims, wherein the first plate comprises

first channels on one side and second channels on the other side.

7. Device as claimed in one or more of the foregoing claims, wherein the plates and the membranes are manufactured from a biocompatible material.

8. Device as claimed in one or more of the foregoing claims, wherein the membranes are made of a microporous material.

9. Device as claimed in claim 8, wherein the microporous material comprises polypropylene.

10. Device as claimed in one or more of the foregoing claims, wherein the plates are manufactured from a plastic.

11. Device as claimed in claim 10, wherein the channels are manufactured by means of a roller embossing, injection moulding or UV embossing.

12. Device as claimed in one or more of the foregoing claims, wherein the plates are manufactured from a metal such as RVS 316, RVS 316L, ASTM F6795 or ASTM F1314-95.

13. Device as claimed in one or more of the foregoing claims, wherein the device comprises a stack of first plates, second plates and membranes for enlarging the blood processing capacity of the device.

14. Device as claimed in one or more of the foregoing claims, wherein the plates and membranes are contained in a housing which also comprises the chambers with the feed and discharge.

15. Device as claimed in one or more of the foregoing claims, wherein the housing holds the membranes and the plates pressed against each other.

16. Device as claimed in one or more of the foregoing claims, wherein the membranes are at least permeable to oxygen and carbon dioxide.

17. Device as claimed in one or more of the foregoing claims, wherein the plates have a thickness of 100 µm to 200 µm and the channels have a depth of 20 µm to 70 µm and a width of 100 µm to 300 µm.

18. Method for processing blood using a device as claimed in one or more of the foregoing claims.

19. Method for assembling a device as claimed in one or more of the claims 1-17, comprising steps for stacking plates and membranes.

20. Method as claimed in claim 19, further comprising steps for assembling stacked plates and a housing and the fixing thereof.

20. Method for manufacturing a plate for use in a device as claimed in one or more of the claims 1-17, comprising steps for arranging micro-ridges in a plate material.

21. Method as claimed in claim 20, wherein the arranging is carried out by means of roller embossing.

22. Method as claimed in claim 20, wherein the arranging is carried out by means of injection moulding.

23. Method as claimed in claim 20, wherein the arranging is carried out by means of UV embossing.

24. Device as claimed in one or more of the claims 1-17, wherein the second channels are suitable for passage of blood processing liquids and the membrane is suitable for passage of substances present in blood for the purpose of cleaning the blood.

25. Device as claimed in claim 24, wherein the liquids are flushing liquids for absorbing blood-contaminating substances present in blood.

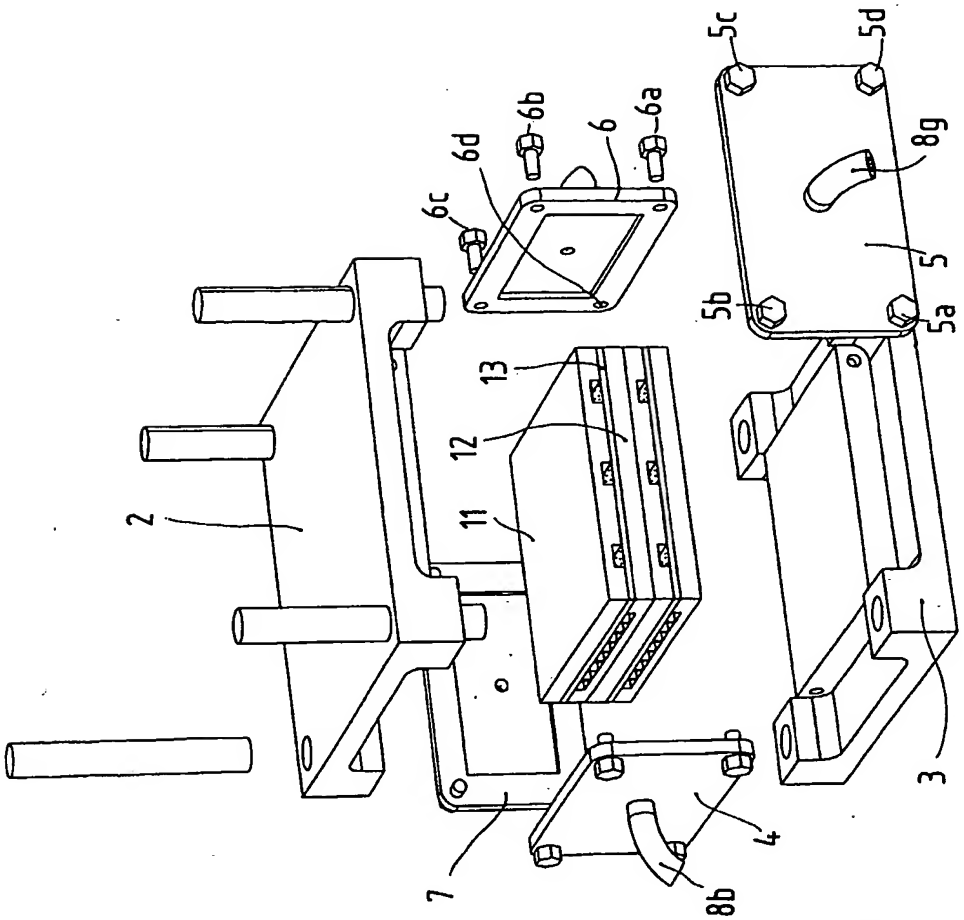


FIG.2

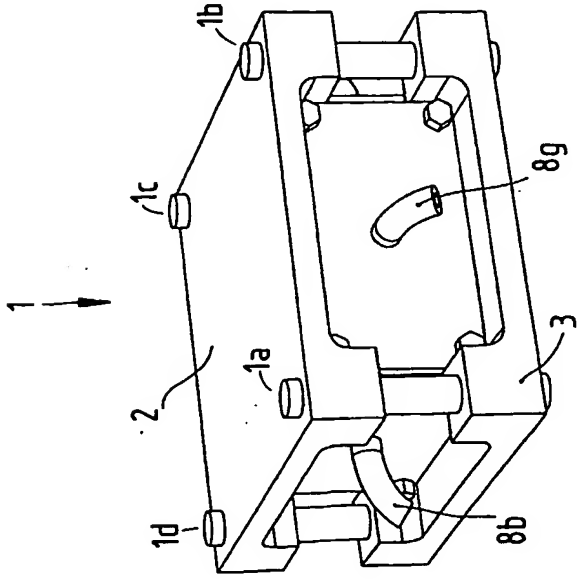


FIG.1

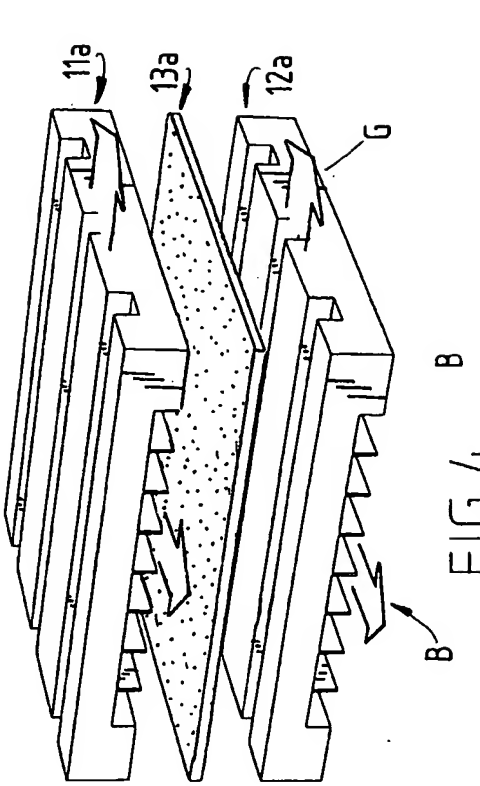


FIG.4

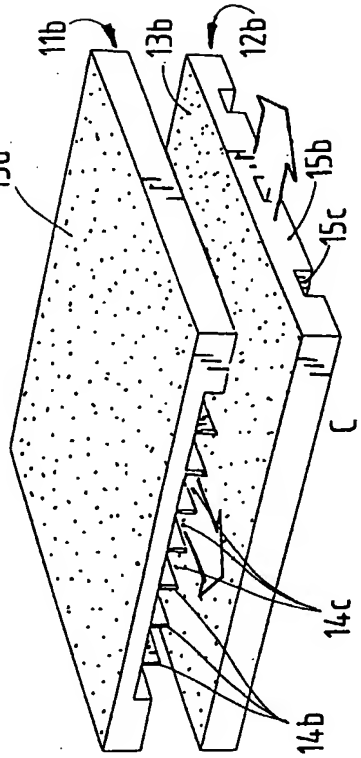


FIG.5

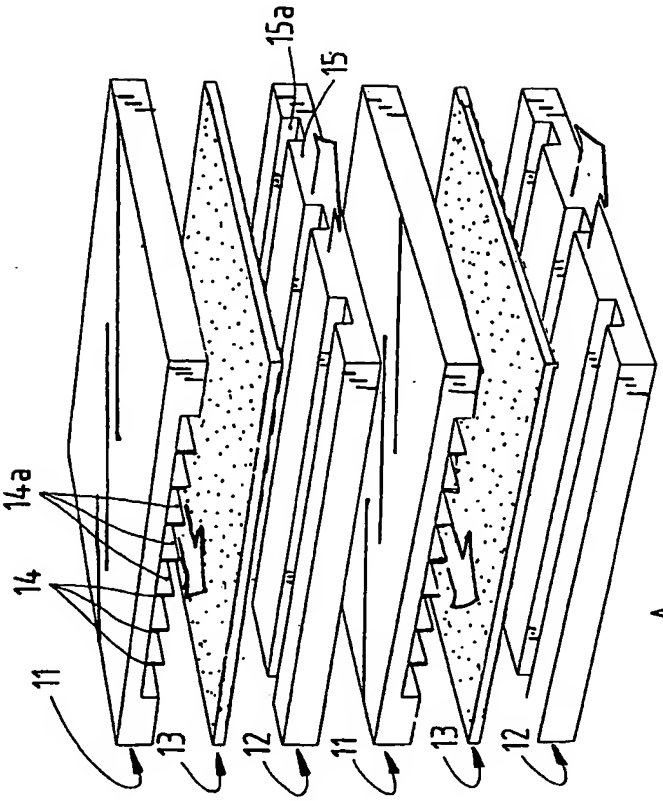


FIG.3

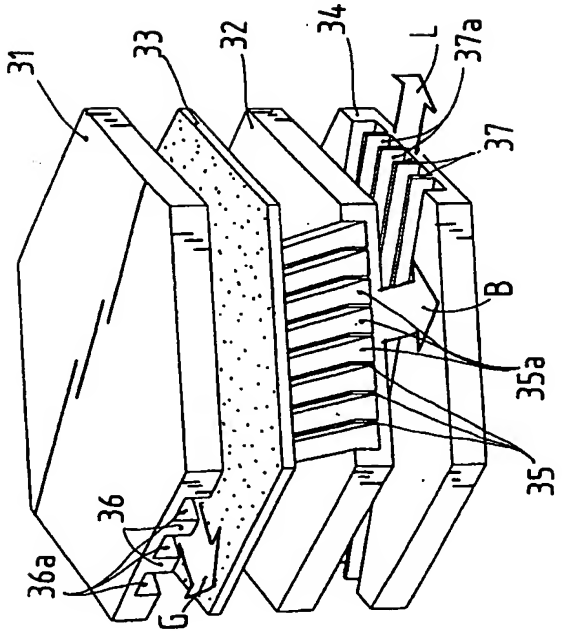
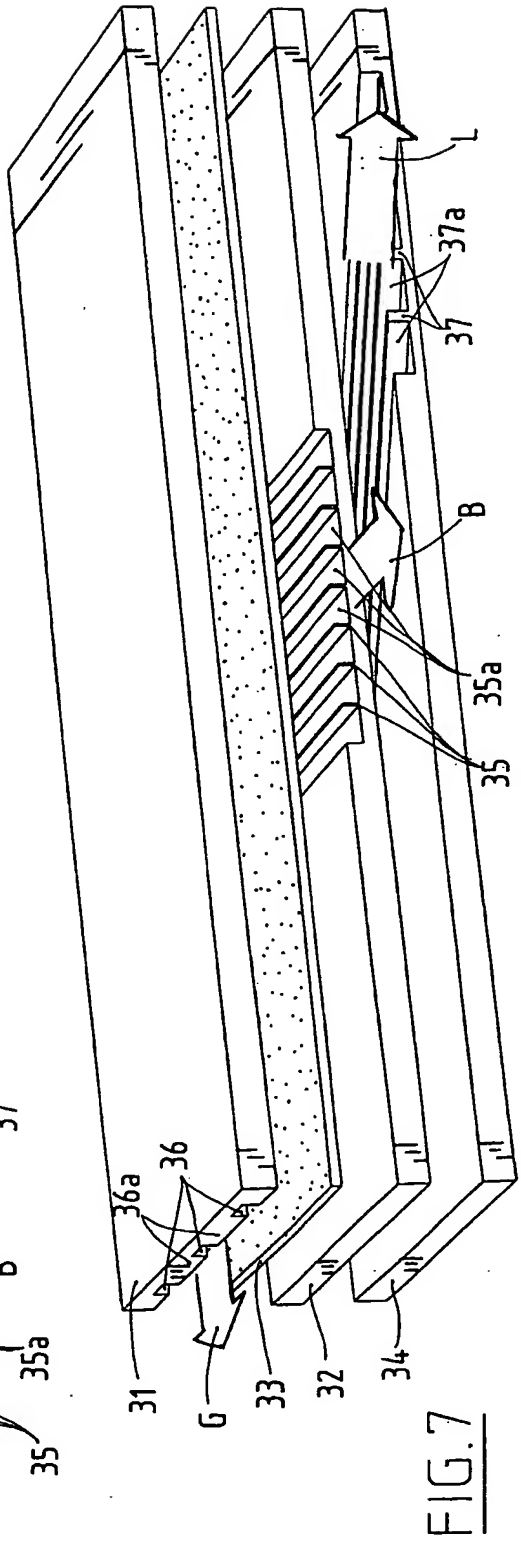

31
33
32
34
L
37a
37
B
35a
35
36
36a
G

FIG.6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35
36a
36
31
G
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32
34

FIG.7

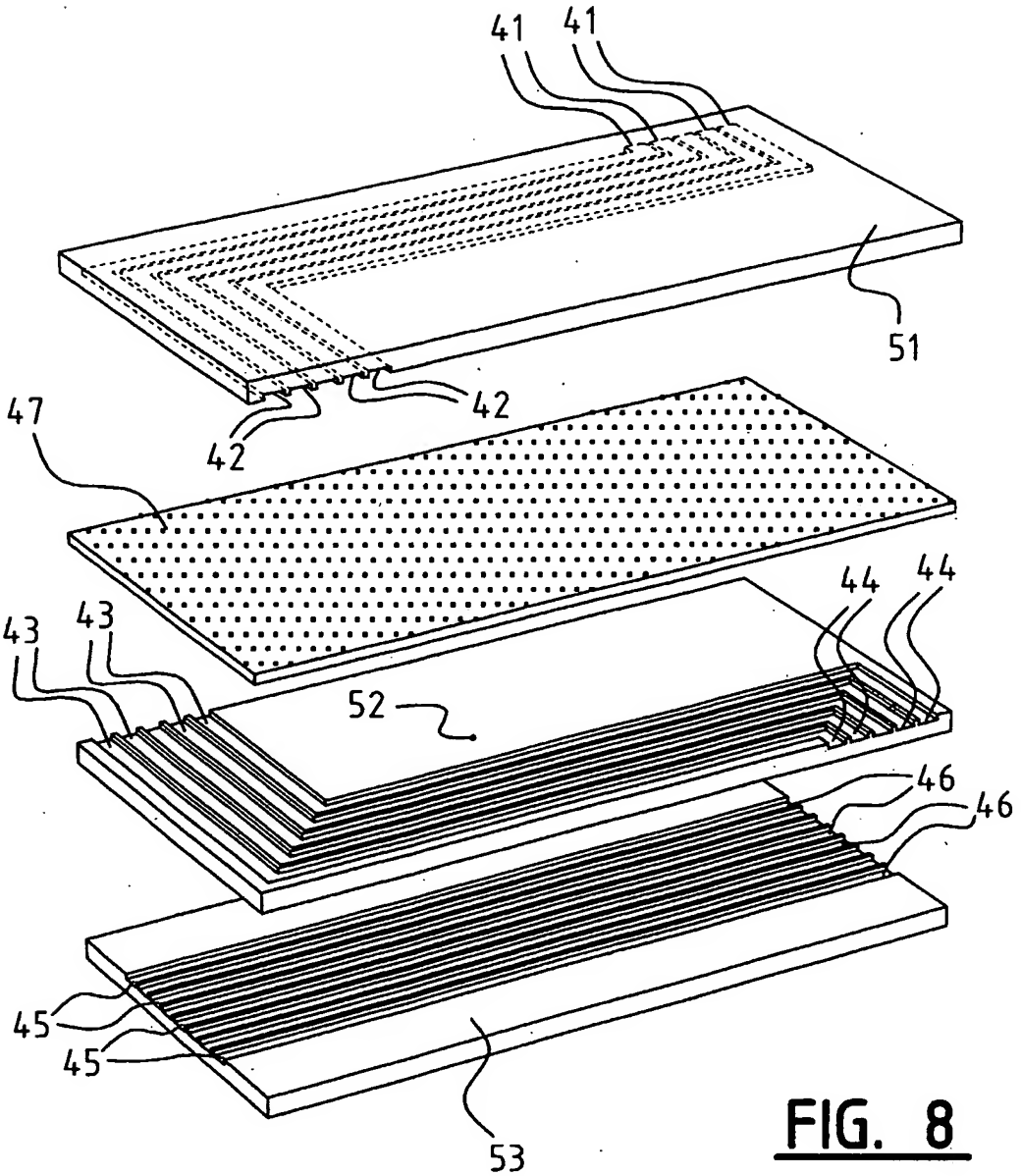

FIG. 8

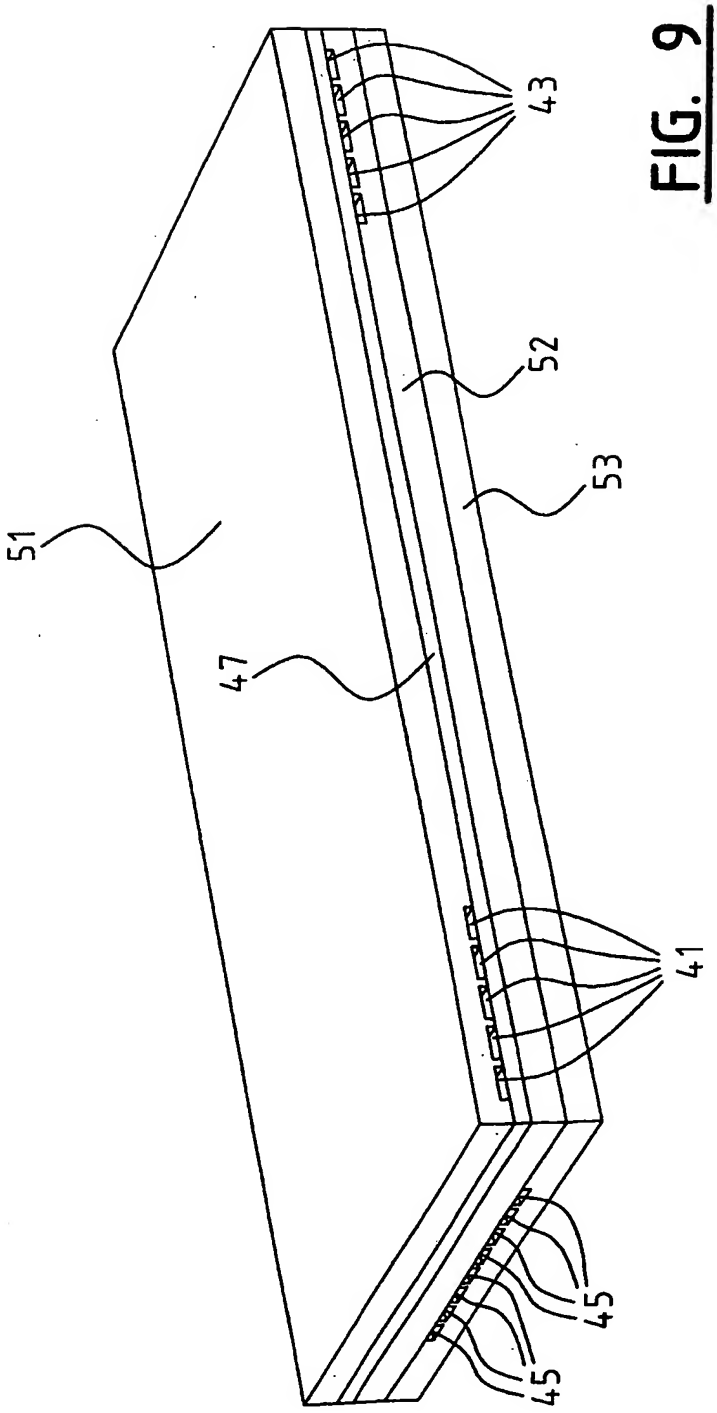

FIG. 9

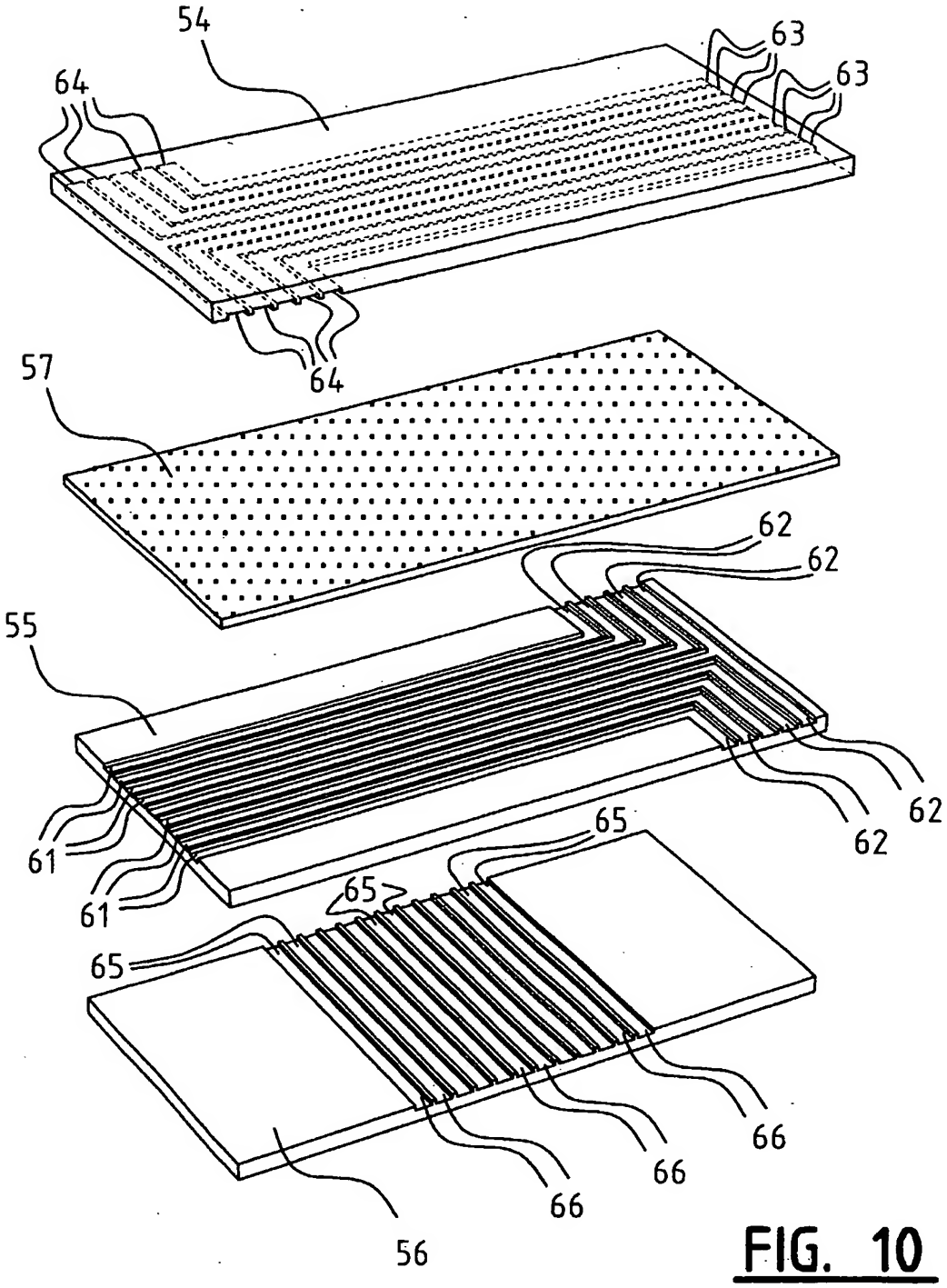

FIG. 10

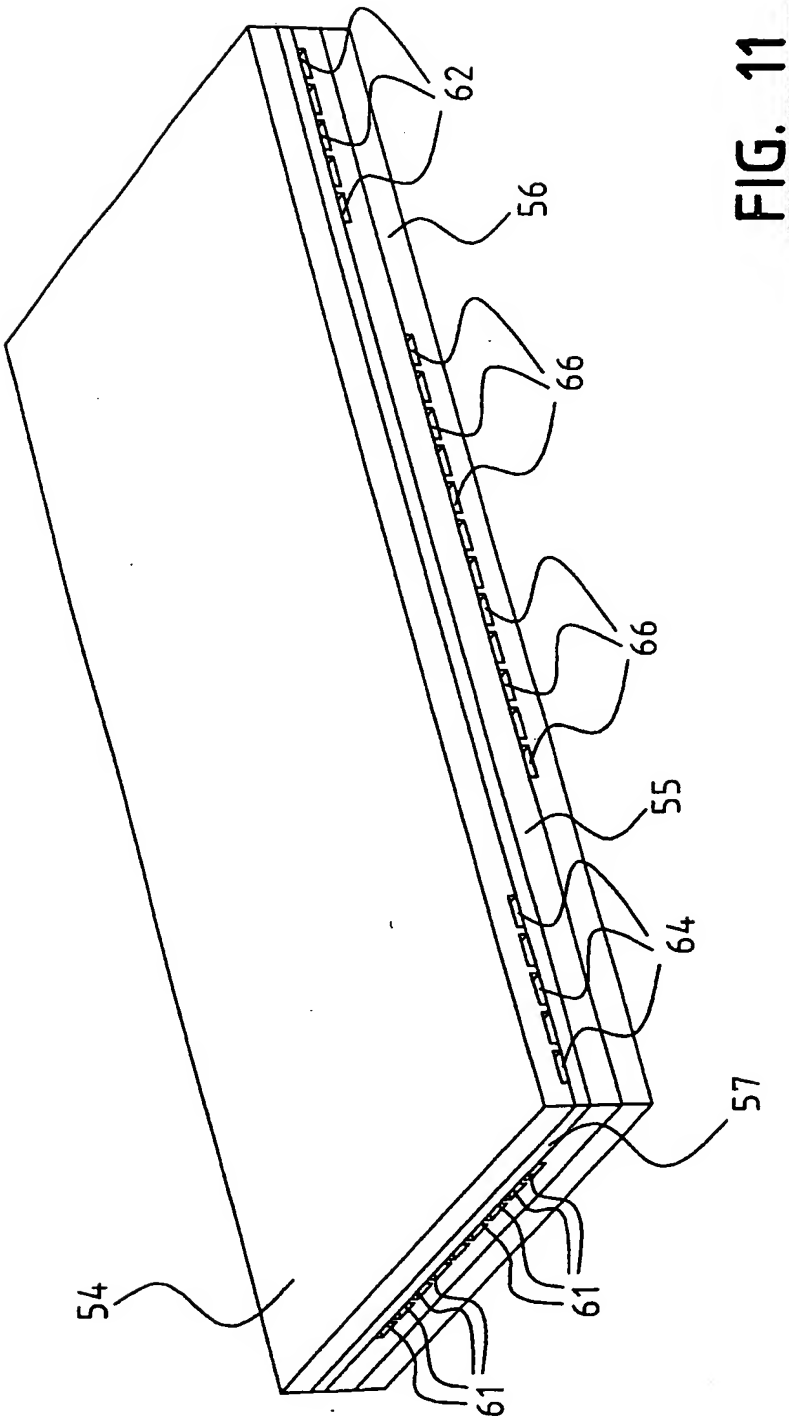

FIG. 11

INTERNATIONAL SEARCH REPORT

PCT/NL 02/00170

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M1/16 B01D71/26 B01D69/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M B01D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 52621 A (BAXTER INT) 21 October 1999 (1999-10-21) page 13, line 27 -page 16, line 1; figures 1,2 page 31, line 27 -page 32, line 1; figure 27 page 38, line 4 - line 6 ---	1-17,19, 20,24,25
X	GB 2 024 653 A (LAVENDER A R) 16 January 1980 (1980-01-16) page 6, line 8 - line 78 page 7, line 108 - line 129 page 7, line 51 - line 66 figures 1,2,4 --- -/--	1-3, 5-17, 19-25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 July 2002	12/07/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lakkis, A

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 47189 A (LIFE SCIENCE HOLDINGS INC) 23 September 1999 (1999-09-23) page 2, line 21 - line 24 page 5, line 12 - line 24; figure 3 page 6, line 31 -page 7, line 2	1-4, 6-17, 19-25
X	US 4 310 416 A (TANAKA YOSHINOBU ET AL) 12 January 1982 (1982-01-12) abstract	20,21
X	US 2 982 416 A (BELL JAMES F) 2 May 1961 (1961-05-02) column 2, line 10 - line 29; figure 1	20,21

INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 18
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/NL 02/00170

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9952621 A	21-10-1999	AU 3743799 A	01-11-1999
		WO 9952621 A1	21-10-1999
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		WO 9947189 A1	23-09-1999
US 4310416 A	12-01-1982	JP 54141386 A	02-11-1979
		JP 1338778 C	29-09-1986
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		JP 61004566 B	12-02-1986
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US 2982416 A	02-05-1961	NONE	